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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/402,093	OHSUYE ET AL.	
	Examiner	Art Unit	
	YONG D. PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-62,64-68,70-73,76 and 78-98* is/are pending in the application.

4a) Of the above claim(s) *84-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-62,64-68,70-73,76,78-81,94-96 and 98* is/are rejected.

7)☒ Claim(s) *82,83 and 97* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/28/08 & 4/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on July 16, 2008, amending claims 54, 64-66, 70-72, 92, and 98, has been entered.

Claims 54-62, 64-68, 70-73, 76, and 78-98 are pending. Claims 84-92 are withdrawn. Claims 54-62, 64-68, 70-73, 76, 78-83, and 93-98 are under consideration.

Election/Restrictions

Applicants elected Group I (claims 54-81 and 94-97) with an election of species, SEQ ID NO:20, which is composed of a protective peptide (amino acids 1-110 of SEQ ID NO:20), helper peptide (amino acids 111-123), and a peptide of interest (amino acids 124-154), wherein said peptide of interest is a GLP-1(7-37) peptide of SEQ ID NO:28.

Claim 93 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic claim.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on October 28, 2008 and April 25, 2008 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

In view of the amendment of claims 54 and 72, the objection to claims 54-62, 64-68, 72-73, 76, 78-81, and 98 have been **withdrawn.**

In view of applicant's argument, the objection to claim 97 has been **withdrawn.**

Claim Objection

Claim 97 is objected to because of the following informalities:

Claim 97, line 19, a conjunction is missing after "step (3)".

Further, in order to improve clarity and achieve uniformity, it is suggested that the phrase "the fusion protein" in line 20 be amended to recited "said fusion protein".

Claim Rejections - 35 USC § 112 – 2nd paragraph

In view of the amendment of claims 54 and 70-72, the rejections of claims 154-62, 64-68, 70-73, 76, 78-81, 94-96 and 98 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-62, 64-68, 70-73, 76, 78-81, 94-96, and 98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 54-62, 64-68, 70-73, 76, 78-81, 94-96, and 98 drawn to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a peptide of interest, a vector and a cell comprising said DNA.

The claims encompass the genus of protective peptides and the genus of helper peptides. While the genus of protective peptides is represented by a single peptide that is a fragment of E. coil 13-galactosidase, other protective peptides and their role in the purification of a peptide of interest are known in the art. Furthermore, the protective peptides are auxiliary to the instant invention. However, the helper peptides are the crux of the invention. The highly variable genus of helper peptides is described by pl that should be between 8 and 12 when a helper peptide is connected to the peptide of interest. The representative species of said genus are limited to the helper peptides that are part of SEQ ID NOs: 20-23, wherein fusion proteins of SEQ ID NOs: 20 and 23 comprise the same helper peptide of 13 amino acids, SEQ ID NO: 22 comprises helper peptide of 13 amino acids that differs from the one in SEQ ID NOs: 20 and 23 by a

single substitution and SEQ ID NO:21 comprises a 16 amino acids helper peptide that is highly homologous with the previous ones. The specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a protective or helper peptide and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other peptide of interest. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of the species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims meet the written description requirement because compliance with the written description requirement is determined irrespective of whether a feature of the claims is “essential” to the invention, so this line of inquiry is irrelevant. Examiner used the word "essential" to stress that while protective peptides are known in art, the genus of helper proteins is not well known.

Applicants argue that the genus of helper proteins does convey distinguishing information about the identity of the claimed helper peptides, such as their relevant structural or physical characteristics because specification provides disclosure of relevant functional characteristic, which follows “directly from the amino acid sequence of the helper peptide”, and a skilled can predict the pI of a peptide from its amino acid

sequence. Examiner respectfully disagrees. While the pI of a peptide can be predicted, the structure of a helper cannot be predicted from a given pI or a given range of pI. The entire highly variable genus is represented by only three helper peptides of similar structure (SEQ ID NOs: 20 and 23 comprise the same helper peptide, supra). The recitation of "helper peptide" having the recited pI fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "helper peptide" having the recited pI, the functional definition of the genus and the recitation of pI or range of pI do not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a few species within the genus. In the instant case the claimed genera of the claims includes species which are widely variant in structure. The claims are drawn to structurally diverse species as it encompasses any or all "helper peptide" having the recited pI. As such, the description of solely functional features present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus.

Hence the rejection is maintained.

Claims 54-62, 64-68, 70-73, 76, 78-81, 94-96 and 98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making derivatives of human GLP-1 using fusion proteins shown at Figures 7, 11-13 (SEQ ID NOs: 20-23), does not reasonably provide enablement for a process of making a GLP-1 derivative recited in the claims using other helper peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 54-62, 64-68, 70-73, 76, 78-81, 94-96 and 98 are directed to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a specific peptide of interest, a vector and a cell comprising said DNA.

Therefore, they are drawn to a method of making of a genus of polypeptides of interest having the specific defined structures, wherein the isoelectric point of said peptide of interest connected to a helper peptide of any structure is between 8 and 12. While the specification teaches a method of making of a highly purified GLP-1 derivative using the specific construct comprising the specific helper peptide, it does not provide any guidance as to a process for producing a highly purified GLP-1 derivative using a helper peptide of an unknown structure. This would involve designing a helper peptide-peptide of interest fusion with the only limitation of having isoelectric point in the wide

range of 8-12. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find the helper peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use the fusion of protective peptide, helper peptide and peptide of interest in a claimed method.

The state of the art is such that it is unpredictable which helper peptides other than the ones present in fusion proteins of SEQ ID NOs: 20-23 should be used. The specification provides no guidance on the matter.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted a priori. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an appropriate purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of a GLP-1 derivative recited in the claims using a helper peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the specification enables a process of using a number of helper peptides reasonably commensurate with the scope of the claims because the specification teaches that all polypeptides having the recited characteristics of a helper peptide may be used in the process and if a reasonable number of the encompassed work in the claimed process, there is no reason to question whether the entire genus of helper peptides is enabled. Examiner respectfully disagrees. The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find helper peptides that changes the characteristics of the peptide of interest to which it is attached to. However, the state of the art is such that it is unpredictable which helper peptides other than the ones present in fusion proteins of SEQ ID NOs: 20-23 should be used. The specification provides no guidance on the matter.

As discussed above, it is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation

would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted a priori. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 72, 73 and 76 remain rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki et al.

Suzuki et al. (US Patent 5,891,671, form PTO-892 mailed May 312, 2007) teach an expression vector comprising a DNA encoding a fusion protein comprising the protective peptide, helper peptide and 7-37 GLP-1 and an E. coil transformed with said vector (columns 5 and 6, columns 17-20, Examples 11-14, claim 13). Said protective peptide is a fragment of E. coil 13-galactosidase that is used in the instant invention and cleavage site between a linker peptide and a peptide of interest is a Kex2 protease cleavage site as in the instant invention. The bond between protective and linker peptides represents another cleavage site.

Absent evidence to the contrary the fusion of the helper peptide and the 7-37 GLP-1 fusion has the requisite pl. They further teach other peptides of interest such as GLP-1 (7-36) NH2 that can be obtained similarly (e.g., column 5, line 22).

The applied reference has a common inventor, Yuji Suzuki, with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims are not anticipated by Suzuki et al. because a skilled artisan would not interpret a “cleavage site” as any peptide bond. Examiner respectfully disagrees. As discussed previously, since the peptide bond between the

protective peptide and the linker can be cleaved by some agent, either a protease or a chemical agent and the claims do not recite a specific cleavage site, said peptide bond between the protective peptide and linker is a cleavage site.

Applicants also argue that that since no linker site is recited in the composition of the pending claims and the '671 patent does not teach or suggest the use of a helper peptide, let alone the order provided", the reference of Suzuki et al. does not anticipate the instant claims. Examiner respectfully disagrees. The "linker site" of Suzuki et al. is construed as a helper peptide since it meets the structural and physical characteristics recited in the claims, i.e. length is within required 5-50 amino acids and pI, absent evidence to the contrary, is within 8-12.

Hence the rejection is maintained.

Allowable Subject Matter

Claims 82-83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652